Prevalence of Depressive Symptoms in Postmenopausal Women with Low Bone Mineral Density and/or Prevalent Vertebral Fracture: Results from the Multiple Outcomes of Raloxifene Evaluation (MORE) Study

STUART L. SILVERMAN, WEI SHEN, MICHAEL E. MINSHALL, SUNNY XIE, and KATHRYN H. MOSES

ABSTRACT. ***Objective.*** To examine the prevalence of depressive symptoms in a cross-sectional study of postmenopausal women with osteoporosis with and without prevalent vertebral fracture.

Methods. Participants were a subset of English-speaking women (n = 3798, mean age 66.7 yrs) from the Multiple Outcomes of Raloxifene Evaluation trial, who had low bone mineral density (BMD) and/or prevalent vertebral fractures. Vertebral fractures were measured at baseline by radiography using a semiquantitative technique. Depressive symptoms were assessed at baseline using the Geriatric Depression Scale (GDS), a valid and reliable scale for depression screening in elderly patients. Women were considered as probably depressed if ≥ 6 symptoms of depression were reported.

Results. Postmenopausal women with prevalent vertebral fracture reported more depressive symptoms as assessed by the GDS than women without prevalent vertebral fracture (1.54 vs 1.26; p = 0.001). There was an absolute increase of 2.5% (p = 0.008) in the prevalence of probable depression (GDS score ≥ 6) in women with prevalent fracture compared to those without prevalent fracture. The prevalence of probable depression was 4.1% among women without prevalent vertebral fracture and 6.6% in women with a prevalent vertebral fracture. The prevalence of probable depression was 3-fold higher in women with at least 3 prevalent vertebral fractures compared to women without prevalent fracture (12.8% vs 4.1%; p < 0.001).

Conclusion. Postmenopausal women with prevalent vertebral fractures had greater prevalence of depressive symptoms and probable depression as assessed by the GDS than women without vertebral fracture with low BMD. The dual diagnosis of depression and osteoporosis may mean worse health outcomes. Patients with prevalent vertebral fractures may be considered not only for interventions that address fracture risk reduction, but also for psychosocial interventions that address depressive symptoms. (J Rheumatol 2007;34:140–4)

Key Indexing Terms:
VERTEBRAL FRACTURE OSTEOPOROSIS DEPRESSION
GERIATRIC DEPRESSION SCALE HEALTH-RELATED QUALITY OF LIFE

More than 75 million people in the United States, Europe, and Japan are affected by osteoporosis. In the European Union, the number of people over 65 years of age with osteoporosis is estimated to rise to more than 26 million women and more than 4 million men by 2050[1]. An estimated 44 million people, 55% of the people aged 50 years and older in the United States, are at risk of either osteoporosis or low bone mass[2]. The lifetime risk of any fracture among Caucasian women over age 50 is nearly 75%[3]. Depression is known to disproportionately affect older patients with chronic illness[4], and is often a comorbid condition with illnesses associated with aging such as type 2 diabetes mellitus[5] and stroke[6].

Osteoporosis can have a significant impact on a patient's psychological health[7] and health related quality of life (HRQOL)[8]. Anxiety, depression, loss of social roles, social limitation, increased disability, and decreased self-esteem are generated and/or enhanced by the limitations imposed from osteoporotic fractures both radiographic and clinical[9-11].

Our group reported the association of prevalent radiographic vertebral fracture and decreased HRQOL in a sub-

From Cedars Sinai Medical Center, UCLA, Greater Los Angeles Veterans Administration Health System, Los Angeles, California; Eli Lilly and Company, Indianapolis, Indiana; Center for Outcomes Research, Fishers, Indiana; Indiana University School of Medicine, Department of Public Health, Indianapolis, Indiana; and Forest Laboratories, Inc., New York, New York, USA.

S.L. Silverman, MD, Cedars Sinai Medical Center, UCLA, Greater Los Angeles Veterans Administration Health System; W. Shen, PhD, Eli Lilly and Company; M.E. Minshall, MPH, Center for Outcomes Research; S. Xie, MS, Forest Laboratories, Inc.; K.H. Moses, MPH, Indiana University School of Medicine.

Address reprint requests to Dr. S.L. Silverman, The OMC Clinical Research Center, 8641 Wilshire Boulevard, Suite 310, Beverly Hills, CA 90211. E-mail: stuarts@OMCresearch.org

Accepted for publication September 26, 2006.

set of a multinational clinical trial of postmenopausal women with osteoporosis with low bone mineral density (BMD) and/or prevalent vertebral fracture[8]. We now report the prevalence of depressive symptoms at baseline in a larger group of English-speaking women enrolled in the same trial. There is a known relationship between depression and osteoporosis, first identified in the late 1980s from semi-structured interviews[10]. Subsequent studies have demonstrated an association between depression and osteoporosis, when quantified as a decrease in BMD[12-16]. However, there are no data on the prevalence of depressive symptoms or probable depression in postmenopausal women with or without prevalent radiographic fractures. This study provided an opportunity to confirm the association between depression and osteoporosis in a large, well characterized international multicenter study and allowed comparisons of prevalence of depression in patients with and without prevalent fracture.

MATERIALS AND METHODS

Subjects. Participants in the Multiple Outcomes of Raloxifene Evaluation (MORE) study included 7705 postmenopausal women at 180 centers in 25 countries, up to 80 years of age[17]. Women were enrolled if they had osteoporosis, as defined by low BMD (T score ≤ –2.5), with or without prevalent vertebral fractures. The women were randomly assigned to one of 3 treatment groups: placebo, 60 mg raloxifene, and 120 mg raloxifene. All subjects also received daily supplements of calcium (500 mg) and vitamin D (400–600 IU)[17].

Women who completed the Geriatric Depression Scale (GDS) and had radiographic assessment of vertebral fractures at baseline (n = 3798) were included in the analysis to examine the prevalence of depressive symptoms in postmenopausal women with low BMD and/or prevalent vertebral fracture (Figure 1). Since the GDS was available only in English and was not translated or validated in any other languages, administration of the GDS was limited to women who read and understood English from the 6 English-speaking countries (United States, Canada, United Kingdom, Australia, New Zealand, and Singapore) taking part in the MORE study.

Vertebral fracture measurements. Radiographs of the lumbar and thoracic spine were obtained at baseline and examined at the quality assurance center (Osteoporosis and Arthritis Research Center, University of California at San Francisco, San Francisco, CA, USA). Radiographs were scored using a semiquantitative scale for each vertebra (T4 to L4) as described[18]. The grading scores were as follows: 0 (no fracture), 1.0 (mild), 2.0 (moderate), or 3.0 (severe) for vertebral fractures. Nonvertebral fractures were assessed by self-report.

Measurement and scoring of the GDS. The GDS is a reliable and valid self-administered measure of the number of symptoms for depressive illness in older adults developed by Yesavage[19,20]. The GDS was designed to be applicable to those patients with physical health problems by excluding somatic items and to provide a simple yes/no format for ease of administration to older persons.

Each of the 15 questions in the GDS corresponded to a depressive symptom. The GDS total score was determined by summing the number of affirmative responses reported for the depressive symptoms assessed by the instrument. The total number of affirmative responses determined the level of depression. A score between 0 and 5 indicated no depression, while a score ≥ 6 indicated probable depression[20]. The GDS is sensitive enough to differentiate further among those who are indicated for probable mild/moderate depression (score = 6–10), or for probable severe depression (score ≥ 11).

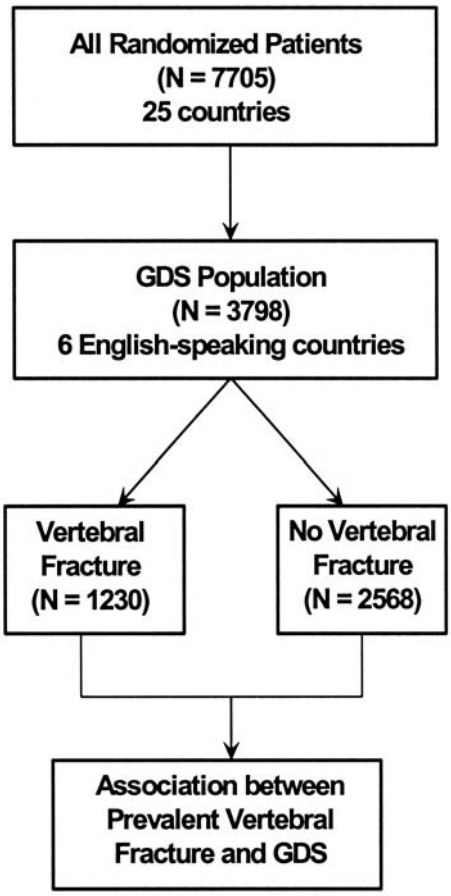

Figure 1. Women included in the analyses of associations between vertebral fractures and Geriatric Depression Scale (GDS).

Statistical analyses. Baseline demographic and clinical characteristics were summarized overall and by presence of vertebral fractures.

To examine the association between the presence of vertebral fractures and total GDS score, the difference in total GDS score between women with and without prevalent vertebral fractures was compared using an analysis of covariance model. In addition, the percentages of women who reached various thresholds of depressive symptoms as measured by the total GDS score were tabulated by presence of vertebral fracture and compared using a logistic regression model. The association between the number of vertebral fractures and the rate of probable depression was evaluated using a logistic regression model. In order to control for possible confounding, all analyses were adjusted for age, country of origin, body mass index (BMI), smoking status, alcohol use, presence of nonvertebral fracture, and lumbar spine BMD.

All differences were tested at a significance level of $p = 0.05$. All analyses were performed using SAS version 6.08 (SAS Institute, Cary, NC, USA)[21].

RESULTS

Demographics. The demographic and clinical characteristics of all participants are shown in Table 1. The 3798 women were predominantly Caucasian (96%) with a mean age of 66.7 years. Of the 3798 women, 1230 (32%) had prevalent vertebral fractures at baseline. As expected, women with prevalent vertebral fractures were older, had a

Table 1. Study population demographics and clinical profile. The differences between women with prevalent vertebral fractures and women without prevalent vertebral fractures were statistically significant ($p < 0.05$) at baseline for the following factors: age, body mass index, years postmenopausal, presence of nonvertebral fracture, and lumbar spine BMD.

Factor	No Vertebral Fracture	≥ 1 Vertebral Fracture	Overall
Sample size, n	2568	1230	3798
Age, mean	65.6	69.0	66.7
Body mass index, mean	25.0	25.7	25.2
Years postmenopausal, median	17.0	22.0	19.0
Current smokers, %	12.6	12.4	12.5
Alcohol, %	23.7	20.8	22.8
Caucasian, %	95.8	95.6	95.8
Country of origin, n			
USA	2003	943	2946
Canada	216	116	332
United Kingdom	177	77	254
Australia	126	69	195
New Zealand	40	23	63
Singapore	6	2	8
Prevalent nonvertebral fracture, %	30.5	43.4	34.7
Lumbar spine BMD, mean T score	–2.1	–2.4	–2.2

higher rate of nonvertebral fractures, and had lower spine BMD scores.

Prevalence of depressive symptoms and probable depression. As shown in Table 2, women with prevalent vertebral fractures reported a significantly higher mean number of depressive symptoms compared to women without prevalent vertebral fractures (1.54 vs 1.26; $p = 0.001$). The prevalence of probable depression (total GDS score ≥ 6) was 4.1% in women without prevalent vertebral fractures compared to 6.6% in women with prevalent vertebral fractures, representing a 2.5% absolute increase in probable depression ($p = 0.008$).

As shown in Figure 2, women with greater numbers of prevalent fractures had greater self-report of probable depression: 4.1% of women without prevalent fracture reported probable depression by GDS as compared to 12.8% of women with 3 or more vertebral fractures, roughly a 3-fold greater prevalence ($p < 0.001$).

Other risk factors were associated with probable depression. BMI, smoking, alcohol use, country of origin, lumbar spine BMD, and age were also found to be associated with increasing numbers of depressive symptoms. All these risk factors, other than lumbar spine BMD, were also associated with a higher rate of probable depression (GDS total score ≥ 6). Prevalent nonvertebral fracture was not associated with increases in GDS scores. Overall, number of vertebral fractures was the best predictor of GDS scores.

DISCUSSION

Prevalent vertebral fractures and depression. Our study indicates that the number of depressive symptoms is associated with greater numbers of prevalent vertebral fractures. Women who had at least 3 prevalent vertebral fractures were more than 3 times as likely to report probable depression, as defined by a total GDS score ≥ 6. Our results indicate significantly greater prevalence for depressive symp-

Table 2. Association of prevalent vertebral fractures with GDS scores. All analyses adjusted for age, country of origin, body mass index, smoking status, alcohol use, presence of nonvertebral fracture, and lumbar spine BMD.

	No Vertebral Fracture n = 2568	≥ 1 Vertebral Fracture n = 1230	p
Overall GDS mean scores	1.26	1.54	0.001
Score ≥ 1, %	53.5	57.3	0.347
Score ≥ 2, %	28.8	34.2	0.017
Score ≥ 3, %	16.4	22.0	< 0.001
Score ≥ 4, %	10.0	14.6	< 0.001
Score ≥ 5, %	6.3	8.9	0.031
Score ≥ 6 (probable depression), %	4.1	6.6	0.008

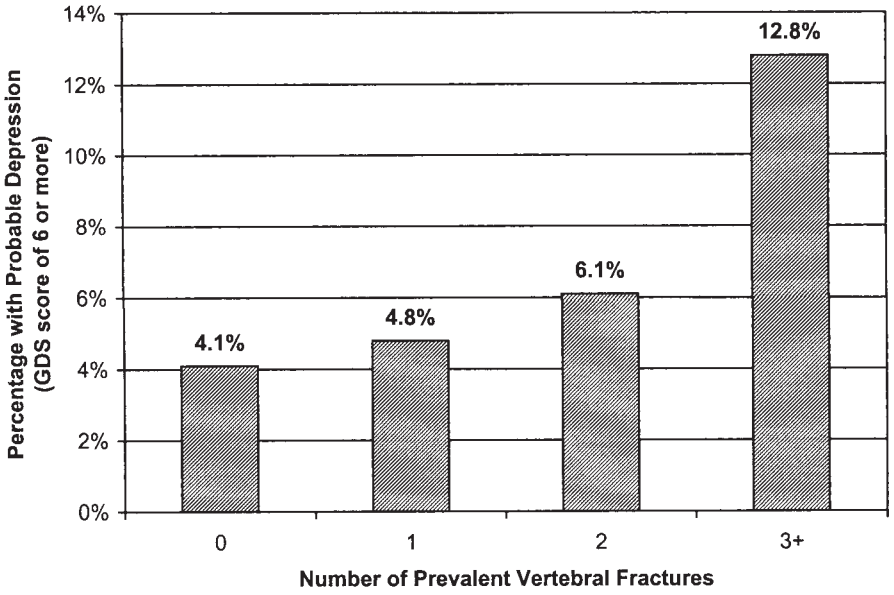

Figure 2. Increased number of prevalent vertebral fractures was associated with higher prevalence of probable depression.

toms with higher numbers of prevalent vertebral fractures; however, many other physical, social, or emotional factors may have an effect on a patient's mental health.

The reason for the greater prevalence of depressive symptoms in postmenopausal women with prevalent vertebral fractures is not known. Whooley, *et al* reported increased incidence of falls in patients with depressive symptoms[16]. Increased falls may lead to fractures. Excessive glucocorticoid excretion as a result of overreactivity of the HPA axis has been described in major depressive disorder[22], and glucocorticoid excess may lead to accelerated bone loss and increased rates of fracture[23].

Lumbar spine BMD. While our study does confirm an association between lumbar spine BMD and higher GDS scores, the findings do not suggest an association between lumbar spine BMD and probable depression. Probable depression was, however, associated with greater numbers of prevalent vertebral fractures.

Influence of depression on health outcomes in women with osteoporosis. Depressive symptoms may worsen health outcomes. Depressive symptoms have been observed to affect diabetic patients' ability to follow self-care treatment plans[24]. Further, depressed individuals may have behaviors that put them at greater risk for fracture, such as sedentary lifestyle and poor eating habits, and may be less likely to be adherent to medications.

Since our study was a subset of the larger MORE study, we were able to take advantage of the opportunity to draw from a very large sample size and, as a result, have a large enough study population from which to examine the association between prevalent vertebral fractures and probable depression.

The MORE study is one of the first large prospective international clinical trials where HRQOL and other psychosocial data were routinely collected on a large sample of postmenopausal women. Data from 2 validated disease-targeted HRQOL questionnaires were collected, including the Osteoporosis Assessment Questionnaire (OPAQ)[25], and the quality of life questionnaire of the European Foundation for Osteoporosis (QUALEFFO)[26,27]. In English-speaking countries, associations between prevalent vertebral fractures and HRQOL were assessed by OPAQ and have been reported in detail[8]. Prevalent vertebral fractures were not only associated with decreases in physical functioning, but were also associated with decreases in emotional status[8]. In the version of OPAQ used in the MORE trial, the depression domain was not included, as the patients completed the GDS, and thus this report completes our analysis of HRQOL in English-speaking countries. Our findings on the association between prevalent vertebral fractures and depression were consistent with these previous findings.

Limitations of the study. Although we adjusted for age, country of origin, BMI, smoking status, alcohol use, presence of nonvertebral fracture, and lumbar spine BMD in our statistical analyses, other variables, such as pain, mobility, and frequency of falls, were not controlled for in the analyses, and these may act as confounding variables. Information about frequency of falls and mobility was not collected in the trial. Many other health and social factors may be related to depression in the elderly; therefore we cannot assume any causal relationships from this study, only associations. Additionally, the study was cross-sectional, not prospective, and therefore we cannot determine which

occurred first, prevalent vertebral fracture or probable depression. No prospective GDS data were collected. Therefore we were unable to observe effects of incident fracture.

Our study population consisted entirely of postmenopausal women, most of whom were Caucasian and all from English-speaking countries. Therefore, the same results should not be extrapolated for men or for women of other races, age groups, or countries of origin. We did not ask about prior history of depression.

Our results from a large, multicenter study confirm that women with prevalent radiographic vertebral fractures reported more depressive symptoms than women without prevalent vertebral fractures. The results also indicate an association between the prevalence of probable depression, as defined by a total GDS score of ≥ 6, and the numbers of prevalent vertebral fractures. Patients with 3 or more fractures had a greater than 3-fold higher prevalence of probable depression.

Other studies have shown that depression is associated with decreased BMD[12-15] and an increased risk for fractures[16]. Our results from the MORE trial also confirm that women with osteoporosis as defined by presence of prevalent fracture have a greater prevalence of depressive symptoms and probable depression. Our results, however, do not tell us whether or not the depressive symptoms are the result of the fractures or whether the depressive symptoms are a contributing factor, or both. The presence of depressive symptoms may negatively influence health outcomes of osteoporosis patients with fracture who may already have decreased health related quality of life. When patients with prevalent vertebral fractures have depressive symptoms, they should be considered not only for interventions that address osteoporotic fracture risk reduction, but also for psychosocial interventions that address depression and its sequelae.

REFERENCES

1. Haaczynski J, Jakimiuk A. Vertebral fractures: a hidden problem of osteoporosis. Med Sci Monit 2001;7:1108-17.
2. National Osteoporosis Foundation website. America's bone health: The state of osteoporosis and low bone mass. Available at: http://www.nof.org/advocacy/prevalence/. Accessed September 28, 2006.
3. Andersson GB, Bostrom MP, Eyre DR, et al. Consensus summary on the diagnosis and treatment of osteoporosis. Spine 1997;22 Suppl:63S-65S.
4. Smith Barusch A, Rogers A, Abu-Bader SH. Depressive symptoms in the frail elderly: Physical and psychosocial correlates. Int J Aging Hum Dev 1999;49:107-25.
5. Grandinetti A, Kaholokula JK, Crabbe KM, et al. Relationship between depressive symptoms and diabetes among native Hawaiians. Psychoneuroendocrinology 2000;25:239-46.
6. Robinson RG, Murata Y, Shimoda K. Dimensions of social impairment and their effect on depression and recovery following stroke. Int Psychogeriatr 1999;11:375-84.
7. Lyles KW, Gold DT, Shipp KM, Pieper CF, Martinez S, Mulhausen PL. Association of osteoporotic vertebral compression fractures with impaired functional status. Am J Med 1993;94:595-601.
8. Silverman SL, Minshall ME, Shen W, Harper KD, Xie S. The relationship of health-related quality of life to prevalent and incident vertebral fractures in women with established postmenopausal osteoporosis: results from the Multiple Outcomes of Raloxifene Evaluation Study. Arthritis Rheum 2001;44:2611-9.
9. Gold DT. The clinical impact of vertebral fractures: quality of life in women with osteoporosis. Bone 1996;18:S185-9.
10. Gold DT. Treatment of osteoporosis: The psychological impact of a medical education program on older patients. J Am Geriatr Soc 1989;37:417-22.
11. Nevitt MC, Ettinger B, Black DM, et al. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. Ann Intern Med 1998;128:793-800.
12. Michelson D, Stratakis C, Hill L, et al. Bone mineral density in women with depression. N Engl J Med 1996;335:1176-81.
13. Coelho R, Silva C, Maia A, Prata J, Barros H. Bone mineral density and depression: a community study in women. J Psychosom Res 1999;46:29-35.
14. Robbins J, Hirsch C, Whitmer R, Cauley J, Harris T. The association of bone mineral density and depression in an older population. J Am Geriatr Soc 2001;49:732-6.
15. Schweiger U, Deuschle M, Korner A, et al. Low lumbar bone mineral density in patients with major depression. Am J Psychiatry 1994;151:1691-3.
16. Whooley MA, Kip KE, Cauley JA, et al. Depression, falls, and risk of fracture in older women. Arch Intern Med 1999;159:484-90.
17. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene. JAMA 1999;282:637-45.
18. Genant HK, Wu CY, Van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137-48.
19. Yesavage J. Geriatric Depression Scale. Psychopharmacol Bull 1988;24:709-11.
20. Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. Clin Gerontol 1986;5:165-73.
21. SAS Institute Inc. SAS/STAT Software. Release 6.08. Cary, NC: SAS Institute; 1994.
22. Swaab DF, Bao AM, Lucasen PJ. The stress system and the human brain in depression and neurodegeneration. Aging Res Rev 2005;4:141-94.
23. Canalis E. Mechanisms of glucocorticoid action on bone. Curr Osteoporos Rep 2005;3:98-102.
24. Rubin RR, Cedanowski P, Egede LE, Lin EH, Lustman PJ. Recognizing and treating depression in patients with diabetes mellitus. Curr Diab Rep 2004;4:119-25.
25. Randell AG, Bhalerao N, Nguyen TV, Sambrook PN, Eisman JA, Silverman SL. Quality of life in osteoporosis: reliability, consist ency and validity of the Osteoporosis Assessment Questionnaire. J Rheumatol 1998;25:1171-9.
26. Lips P, Cooper C, Agnusdei D, et al. Quality of life as outcome in the treatment of osteoporosis: the development of a questionnaire for quality of life by the European Foundation for Osteoporosis. Osteoporosis Int 1997;7:36-8.
27. Oleksik A, Lips P, Dawson A, et al. Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. J Bone Miner Res 2000;15:1384-92.